Validating Modeling & Experimental Methods to Enable Drug Discovery
NIST April 19th-21st 2006

Agenda

April 19th Evaluation of Computational & Experimental Methods

Breakfast 8.00-8.30AM

Morning-Session

8.30-8.45
Introductory comments and welcome
(Willie May, Director, Chemical Science & Technology Laboratory, National Institute of Standards & Technology)

8.45- 9.15
Workshop shop aims & objectives
(Anne Chaka, National Institute of Standards & Technology)

9.15-10.00
Overview & challenges of three broadly applicable experimental technologies for quantitative analysis of small molecule-protein interactions
(Michael Doyle, Bristol-Myers Squibb)

BREAK 10.00-10.30AM

10.30 -11.00
Applications of Isothermal titration calorimetry during small molecule lead identification and optimization
(Rachel Kroe, Boehringer Ingelheim Pharmaceuticals)

11.00 –11.30
Use of SPR methods in drug discovery: specific examples of small molecule-protein interactions

(Mark Witmer, Bristol-Myers Squibb)

11.30 –12.00
ThermoFluor(r):using perturbations in protein thermal stability to measure binding interactions

(Matthew Todd, Johnson & Johnson Pharmaceutical Research and Development L.L.C.)

Lunch 12.00-1.00PM

Afternoon-Session

1.00-2.00
The GSK Docking Evaluation: Would we do it the same next time?"
(Martha Head, GlaxoSmithKline)

2.00-4.30 **Parallel Breakout Sessions (3.00-3.30 Coffee Break, Lecture-Room-B)**
1:Docking methodologies, can we set standards for evaluations?
(Martha Head & Greg Warren, GlaxoSmithKline)

2:Experimental techniques: limitations & uncertainty in measurements
(*John Marino & Fred Schwarz, National Institute of Standards & Technology)*

3:Scoring functions & force fields: **Why do they fail, how are they improved?**
(Tom Halgren, Schrodinger and Scott Brown Abbott labs.)

4.30-6.00: **Presentation of results from breakout sessions**

April 20th New Methods & Technologies for Exploration of Molecular Recognition Events

Agenda

Breakfast 8.15-8.45AM

Morning Session

8.45-9.30**: Challenges in the calculation of binding affinities**
(Michael Gilson, Center for Advanced Research in Biotechnology)

9.30-10.00: **Free energy perturbation calculations: improved capabilities, important cautions.**
(Michael Shirts, Columbia University)

Break 10.00-10.30AM

10.30-11.00: **How well does Poisson-Boltzmann solvent agree with explicit solvent? A quantitative analysis.**
(Ray Luo, University of California, Irvine)

11.00-11.30: **Overview of the CHARMM all-atom force fields including the additive & classical Drude polarizable models**
(Alex MacKerell, University of Maryland Baltimore)

11.30-12.00:**The role of Quantum Mechanics in structure-based design**
(Kenneth Merz, University of Florida)

Lunch 12.00-1.00PM

Afternoon Session

1.00-1.30: **Overview of solvation methods**
(Anthony Nicholls, Openeye Scientific Software)

1.30-2.00: **Measuring protein pKa's**
(Jan Jensen, University of Iowa)

2.00-2.30: **Using ion-water clusters to calculate acid dissociation constants.**
(Casey Kelly, University of Minnesota)

Break 2.30-2.45PM

2.45-3.15: **Computations of absolute binding free energy with molecular dynamics simulations**
(Benoit Roux, University of Chicago)

3.15-3.45: **Sensitivity analysis and drug design**
(Chung Wong, University of Missouri-Saint Louis)

3.45-4.15: **Using MD simulations for lead optimization & determination of ligand-receptor structure**
(Carlos Simmerling, Stonybrook University)

4.15-5.45: **Breakout Session & Discussion**
Toward accurate calculation of binding affinities
(Kenneth Merz, University of Florida & Michael Gilson, Center for Advance Research in Biotechnology)

Conference Dinner
Hilton Hotel (620 Perry Parkway, Gaithersburg) Cash Bar 6-6.45PM, Dinner 6.45PM

April 21st Physical Property Measurements

Breakfast 7.45-8.00AM

Morning Session

8.00-8.15
Session Introduction and Overview of Property Measurements

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(Anthony Nicholls (Openeye Scientific Software) & Christopher Bayly (Merck-Frosst)

8.15-9.45
Property Measurements: The value & intricacies (3X30 minutes)

- **Tautomer Ratios** *(Peter Taylor, Astra-Zeneca (retired)*
- **ADME Properties** *(David Leahy, Cyprotex)*
- **Free energies of transfer from gas to solution**
  Peter Guthrie, University of Western Ontario

9.45-10.15
Experimental capabilities in NIST 838.07-thermophysical properties (of really) small molecules. *(Mark Mclinden, National Institute of Standards and Technology)*

Break 10.15-10.45AM

10:45-12.00
Discussion *(Theory panelists: Anthony Nicholls (Openeye Scientific Software), Christopher Bayly (Merck-Frosst), Wolfgang Damm (Schrodinger) et.al.,)*

- **Question 1: What do we want the data for?**
  - **Better predictive models**
  - **Force Field development**
  - **Scoring**
  - **Better physical models**
- **Question 2: What proposed properties are:**
  - **Doable**
  - **Useful**
  - **Vital**
- **Question 3: What else should we be considering?**
  - **Properties**
  - **Experimental techniques**

- 2 min to each theory panelist and speaker, then open

Lunch 12-00-1.00PM

Afternoon session
1.00-3.00:
Breakout & Discussion Chemical Collections Session:
Present chemical wish list with desired properties and justification
(Chris.Bayly, Anthony Nicholls, Peter Guthrie, Peter Taylor, others) (10 min each)

- experimentalists: reality check on wish lists (5 min each)
- discussion, prioritization

Click here to see sample chemical structures:
Hydrocarbon compounds
Functionalized compounds
Heterocyclic compounds

3.00-5.30
Proposals, Outcomes and road maps *(Anne Chaka (NIST)*

Workshop Close (5.30PM)